## CHANGES IN 5-HYDROXYTRYPTAMINE RECEPTOR SUBTYPES IN DISEASED HUMAN EPICARDIAL CORONARY ARTERIES.

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5-hydroxytryptamine (5-HT) may have an important role in the mediation of coronary artery vasospasm. There has been no attempt to characterise the nature of the receptors that mediate the actions of 5-HT on human coronary arteries, or to examine the effect of tissue pathology on the receptor subtypes. Experiments were performed using 138 segments of epicardial coronary artery used 1-8h after removal from 21 patients (2-66 years) undergoing heart transplantion. Ring segments were suspended in a 5ml organ bath containing a modified Tyrodes solution, at 37°C and gassed with 95%/5% $O_2/CO_2$. 5-HT and (±)-alpha-methyl-5-HT (a-me-5-HT) a selective 5-$HT_2$ receptor agonist, contracted vessel segments from normal arteries as well as those affected by atherosclerosis. GR43175 a selective 5-$HT_1$-like receptor agonist contracted healthy arteries to 30%, and diseased arteries to 60% of the effect of a-me-5-HT. The maximum effect of the a-me-5-HT was significantly reduced ($p<0.05$) in diseased arteries, as was the effect of 90mM potassium indicating a decreased contractability of the smooth muscle. However, the response to the 5-$HT_1$-like receptor agonist GR43175, was unchanged in the normal diseased arteries. Furthermore, this preservation of response in diseased arteries was found to occur preferentially in segments just distal to areas of atheromatous lesions. No relaxations were observed for any of the 5-HT agonists in pre-constricted artery segments. It is concluded that 5-HT acts on both 5-$HT_1$like and 5-$HT_2$ receptors, and that the 5-$HT_1$-like receptors are relatively up-regulated in arteries affected with atherosclerosis, and that this is found in areas where vasospasm usually occurs.

## ACUTE INTRAVENOUS BETA BLOCKADE WITH ESMOLOL IN CARDIAC PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

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Patients with chronic obstructive pulmonary disease (COPD) often have cardiac indications for beta blockade, but the possible adverse effects of these drugs on their lung disease is not well defined. We prospectively studied the safety and efficacy of acute intravenous administration of esmolol (8-24 mg/min) in 33 pts with COPD and active cardiac problems (angina, hypertension, recent myocardial infarction or arrhythmia). Twenty pts (61%) had a significant bronchodilator response to albuterol at baseline evaluation. All bronchodilators were withheld before beta blockade. During esmolol infusion, resting heart rate decreased from 85±3 (mean ±SEM) to 69±2 ($p<.01$) and blood pressure decreased from 127±3/72±2 to 108±3/64±2 ($p<.01$). Esmolol was well tolerated, with no episodes of wheezing or dyspnea. Moreover, there was no significant change in FEV1 (1.64±.10 to 1.59±.10), vital capacity (2.31±.15 to 2.31±.15) or peak expiratory flow (4.11±.31 to 3.73±.31) with treatment. FEV1 decreased > 20% in 2 pts, but both were asymptomatic. Subsequently, oral beta blockers were initiated in the remaining 31 pts.

**CONCLUSION:** Short term beta blockade with esmolol can be safely achieved in cardiac pts with COPD.

## CORONARY ARTERY STENOSIS DILATATION AND HAEMODYNAMIC EFFECTS OF HUMAN-ALPHA CALCITONIN GENE-RELATED PEPTIDE IN ISCHAEMIC HEART DISEASE

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To investigate the effect of human-alpha calcitonin gene-related peptide (CGRP) on ischaemic threshold (1mm ST segment depression) at exercise testing and cardiovascular haemodynamics at angiography, 6 patients with effort angina (aged 55-67 years, mean 59.7), and normal LV function (at angiography ) received intravenous infusions of placebo and CGRP at 1.15 ug/min for 10 minutes before and during exercise testing to the modified Bruce protocol. Maximum rate pressure product (RPP) achieved was 238.2 ± 83.7 units and 264.0 ± 80.5 units ($p<0.05$) with placebo and CGRP respectively. There was no significant difference in the time or RPP to ischaemic threshold and in the maximum exercise duration. AO and PA pressures, LV pressure (catheter tip manometer) and cardiac output (by thermodilution, and oxygen content) were measured. Heart rate was fixed below the ischaemic threshold (as assessed by exercise test) by atrial pacing up to 10 beats/min above the peak heart rate attained during previous CGRP infusion at rest. CI (by oxygen content) was 2.75 ± 0.74 and 3.23 ± 0.76 l/min/$m^2$ ($p<0.05$), stroke volume index was 27.4 ± 8.9 and 31.8 ± 8.2 ml/$m^2$ ($p<0.05$), systemic vascular resistance index was 44.6 ± 14.4 and 34.6 ± 15.6 units/$m^2$ ($p<0.05$), and mean AO pressure was 118.5 ± 13.1 and 109.6 ± 79.7 mmHg ($p<0.05$) after five minutes of placebo and CGRP infusions respectively. There was no significant change in mean PA pressure, pulmonary vascular resistance, LVEDP or rate of change of LV pressure (dP/dt). Quantitative analysis of selected coronary artery stenoses confirmed an increase in stenosis diameter of 1.16 ± 0.16 mm to 1.52 ± 0.30 mm (30.7% increase) ($p<0.05$), and in reference diameter of 2.16 ± 0.30 to 2.54 ± 0.37 mm (13.4% increase) ($P<0.05$) on placebo and CGRP respectively.
Intravenous CGRP increases maximum workload achieved but not maximum exercise duration with no demonstrable effect on ischaemic threshold on exercise. Intravenous CGRP dilates both stenosed and normal coronary arteries at rest with an overall increase from 54% to 60% in stenosis diameter. CGRP is a potent systemic arterial vasodilator with no detectable negative inotropic effect in patients with ischaemic heart disease but normal LV function.

## HEMODYNAMIC EFFECTS OF DOPEXAMINE IN PATIENTS WITH CORONARY ARTERY DISEASE

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Dopexamine hydrochloride (D) is a new inotropic vasodilator with beta-2 and dopaminergic (DA1) agonist actions potentially useful for treatment of low cardiac output states. We studied the hemodynamic effects of saline (S), D 1 ug/kg/min (D1) and D 3 ug/kg/min (D3), infused sequentially for 15 minutes in 21 pts with coronary artery disease (mean age=57 years, mean ejection fraction=42%).
Results: Heart rate rose (S to D1 = 70 to 76 beats/min***, D1 to D3 = 76 to 88***). LV stroke work index rose (S to D1= 44 to 51 g/m*, D1 to D3 = 51 to 56**) with no change in LVEDP, indicating improved contractility. End-systolic volume index fell (S to D1 = 45 to 39 ml/m2*, D1 to D3 = 39 to 35*) and maximum positive dP/dT rose (S to D1 = 1294 to 1597 mmHg/s**, D1 to D3 = 1597 to 2199***). Diastolic indices showed decreased relaxation constant (T1/2)(S to D1 = 48 to 44 msec[N.S.], D1 to D3 = 44 to 37*) and mean filling rate rose (S to D1 = 0.013 to 0.018 /sec/beat/min[N.S.], D1 to D3 = 0.018 to 0.021*) and maximum negative dP/dT rose (S to D1 = -1467 to -1653 mmHg/s*, D1 to D3 = -1653 to -1898**). CI increased (S to D1 = 2.6 to 3.2 l/min/m2***, D1 to D3 = 3.2 to 4.0***) indicating no flattening of the dose response curve within this range. Systemic vascular resistance index fell markedly with D1 (S to D1 = 3356 to 2318 dyne.sec.cm-5/m2***) with little addditional decrease at D3 (D1 to D3 = 2318 to 2252***).
Conclusions: 1. D is a potent inotropic agent with vasodilator action.
2. Near maximal vasodilation occurs with low doses of D (D1) while the higher dose (D3) causes incremental increase in myocardial performance.
3. The combination of inotropic and vasodilator properties makes it suitable for therapy of cardiac failure and other low output states.
[* $p < 0.01$, ** $p < 0.001$, *** $p < 0.0001$.]